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Unilateral relapsing purpura on the leg as a first manifestation of IgG lymphoplasmacytic lymphoma

Ieva Saulite · Lukas Graf · Michael Giger · Ilona Hartmane · Eva Markert · Marcus Schittenhelm · Emmanuella Guenova · Antonio Cozzio

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Purpura may initially be the only manifestation of type I cryoglobulinemia [1–3].

Purpura or petechiae typically have an intermittent relapsing course but in type I cryoglobulinemia, necrotic lesions are common. Other skin manifestations of type I cryoglobulinemia include Raynaud's phenomenon, cold-induced pseudourticaria, and livedo [1, 2, 4].

Cutaneous symptoms associated with type I cryoglobulinemia are attributed to cold-induced intravascular precipitation of monoclonal immunoglobulins (mIg), followed by thrombotic obstruction of the vessels, and ischemia/necrosis of the underlying skin [1, 2, 5]. Suspecting a differential diagnose of type I cryoglobulinemia in case of purpura requires further investigation for early recognition of an underlying hematological disorder [4].

I. Saulite (✉) · A. Cozzio
Department of Dermatology, Venerology and Allergology, Kantonsspital St. Gallen, St. Gallen, Switzerland
ieva.sauliite@gmail.com

L. Graf
Center for Laboratory Medicine, Hemophilia and Hemostasis Center, St. Gallen, Switzerland

M. Giger · M. Schittenhelm
Department of Medical Oncology and Hematology, Kantonsspital St. Gallen, St. Gallen, Switzerland

I. Hartmane
Department of Dermatology and Venerology, Riga Stradins University, Riga, Latvia

E. Markert
Institute of Pathology, Kantonsspital St. Gallen, St. Gallen, Switzerland

E. Guenova
Department of Dermatology, Lausanne University Hospital (CHUV) and Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland

Case representation

A 52-year-old woman was referred to our dermatology department with a sudden occurrence of painful superficial nonpalpable purpura on her left knee (Fig. 1a). The purpuric lesions persisted for several hours and then resolved spontaneously without any treatment (Fig. 1b) but relapsed daily. Initially, no association to causative agents including exposure to cold, trauma, or other external factors could be identified. Routine physical examination was otherwise unremarkable. There were no chronic diseases in the personal medical history of the patient, and she did not take any medications.

Initial laboratory investigation of complete blood count showed in normal range as follows: white blood cell count (WBC) 4.2 g/l, hemoglobin 126 g/l, platelets 270 G/l, and absolute neutrophil count (ANC) 2.0 G/l. Serologic tests for connective tissue diseases including ANAs, ANCAs, ENAs, anti-Sm, rheumatoid factor, complement C3, and C4 were within a normal range.

Histopathologic examination of skin biopsy was compatible with occlusive vasculopathy depicting partially congested capillaries with fresh platelet-aggregates and thrombi without any morphologic peculiarities of vasculitis (Fig. 2). Direct immunofluorescence of the skin biopsy detected intraluminal C1q aggregates.

Further diagnostic workup of the occlusive vasculopathy included coagulation testing which revealed a positive lupus anticoagulant (normalized dRVVT

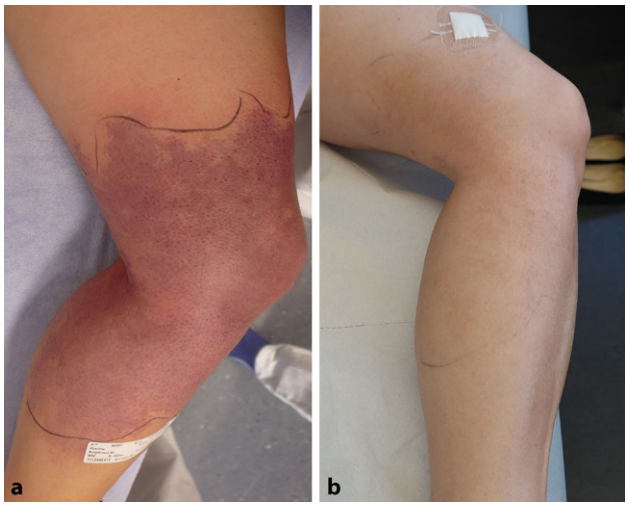

Fig. 1 **a** Clinical manifestation with a sudden occurrence of painful, superficial, nonpalpable purpura on her left knee. **b** Within 3–4 h, the purpuric lesions spontaneously resolved

ratio LA: 1.23, cut-off < 1.10), but other antiphospholipid–antibodies (anti-cardiolipin IgG/IgM, anti-beta2-glycoprotein IgG/IgM) were negative. Hepatitis serology for HBV and HCV as well as HIV1/2 testing was inconspicuous. Serum concentration of immunoglobulin levels showed increased IgG (18.3 g/l, normal range: 6.9–14 g/l), normal IgA (1.1 g/l, normal range: 0.3–2.1 g/l), and IgM (3.3 g/l, normal range: 0.3–2.1 g/l). In serum electrophoresis and immune fixation, a monoclonal gammopathy with an lgG kappa M-protein was observed (14.5 g/I), increased serum-free kappa light chains 34.2 mg/l (normal range: 3.3–19.4 mg/l), and kappa/lambda ratio 2.71 (0.26–1.65). Work-up for cryoglobulins revealed a monoclonal IgG kappa compatible with type I cryoglobulinemia. In patients with IgG cryoglobulinemia around one-third are considered monoclonal gammopathy of undetermined significance (MGUS), one-fifth multiple myeloma (MM), around 8% chronic lymphocytic leukemia (CLL), and the rarest is lymphoplasmacytic lymphoma (LPL) at 3% [3, 6].

Bone marrow biopsy revealed an approximately 10% infiltration with clonal B cell population consistent with lymphoplasmacytic lymphoma. Molecular diagnostics confirmed a monoclonal population with an immunoglobulin heavy chain gene rearrangement: *IgH FR1 311 bp, IgH FR2 246 bp, IgH FR3 106* bp, each of them clonal (mono-allelic). Fluorescence in situ hybridization (FISH) demonstrated no *IgH* rearrangement, the lymphatic next generation sequencing (NGS) panel revealed *MYD88 p. L265P (c.794T > C)*.

Computed tomography examination of neck–chest–abdomen demonstrated no lymphadenopathy and no organomegaly.

MRI of the lower extremities demonstrated normal findings of both knee joints with normal perfusion of the femoropopliteal arteries without evidence of arterial or venous vessel occlusion.

Based on skin histology, serum electrophoresis and immune fixation, bone marrow histopathologic and molecular examination, the diagnosis of type I cryoglobulinemia presenting with purpura due to lymphoplasmacytic lymphoma, a rare B-cell disease described by the malignant accumulation of monoclonal B cells, lymphoplasmacytic cells, and plasma cells in the bone marrow and other tissues [7, 8] was established. The most frequent symptoms in patients with LPL are fatigue related to anemia, typical B-symptoms, sensory neuropathy in the lower extremities, and symptoms due to hyperviscosity including nasal bleeding, blurred vision, and recurrent headaches. Other typical findings include lymphadenopathy and hepatosplenomegaly. Only rarely, as in our case, are clinical manifestations associated with cryoglobulinemia and purpura of the lower extremities. The occurrence of spontaneous severely painful recurrently relapsing purpura progressed with time, appearing daily, and persisting for many hours a day on large skin areas. Before establishing the diagnosis, empiric anticoagulation was initiated which did not improve the recurrent onset of purpura.

Among the commonly used therapies are alkylators (bendamustine or cyclophosphamide) or proteasome inhibitors (bortezomib, carfilzomib, or ixazomib) in combination with the anti-CD20 monoclonal antibody rituximab [7].

In our patient, therapy with rituximab/bendamustine was initiated (total 6 cycles) and showed good clinical response leading to complete clearance of cutaneous manifestations, and normalization of IgG and lupus anticoagulant. In general, overall response rates for the combinations range from 80% to 90%, major response rates range from 50% to 70%, and median progression-free survival varies from 3 to 5 years when used as first-line treatment [8].

Conclusion

Early recognition of type I cryoglobulinemia followed by diagnostic workup is important to identify and treat the possible underlying hematological malignancy, thus indirectly treating cryoglobulinemia, and the associated cutaneous, neurological, and renal manifestations. The treatment in patients with symptomatic cryoglobulinemia type I depends on the associated lymphoproliferative disorder.

Author Contribution I.S. was involved in the analysis of case data, literature review, drafting and revision of the manuscript, and final approval of the report. L.G., M.G., I.H., E.M., M.S., E.G., and A.C. were involved in case analysis, revision of the manuscript, and final approval.

Declarations

Conflict of interest I. Saulite, L. Graf, M. Giger, I. Hartmane, E. Markert, M. Schittenhelm, E. Guenova and A. Cozzio declare that they have no competing interests.

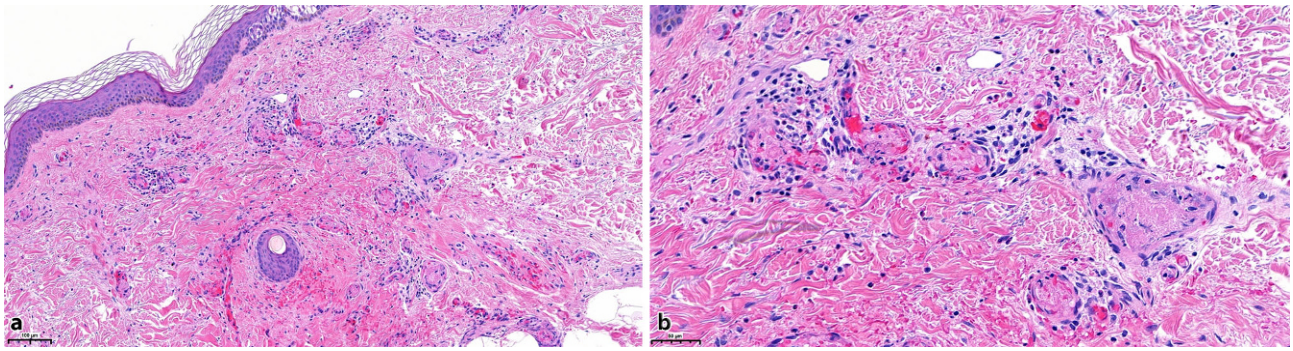

Fig. 2 Histopathologic examination of skin biopsy was compatible with occlusive vasculopathy depicting partially congested capillaries and fresh platelet-aggregates, thrombi without any morphologic peculiarities of vasculitis; hematoxylin and eosin, **a** scale bar = 100 µm and **b** scale bar = 50 µm

Ethical standards Ethical approval is not required for this retrospective, observational case study in accordance with local guidelines by the Ethics Committee of the Canton of St. Gallen. The authors affirm that human research participant provided informed consent for publication of the images in Figs. 1 and 2.

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